EXHIBIT A

PATENT COOPERATION TREATY

9/19

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

To:

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Date of mailing *(day/month/year)*	8 August 2005 (08.08.2005)
Applicant's or agent's file reference: P1495	**FOR FURTHER ACTION** See paragraph 2 below
International application No.: PCT/BR 2005/000036	International filing date *(day/month/year)*: 18 March 2005 (18.03.2005)
	Priority Date *(day/month/year)*: 18 March 2004 (18.03.2004)
International Patent Classification (IPC) or both national classification and IPC: A61K 38/17	
Applicant: Fundacao Oswaldo Cruz - Fiocruz	

1. This opinion contains indications relating to the following items:

- ☒ Cont. No. I — Basis of the opinion
- ☐ Cont. No. II — Priority
- ☒ Cont. No. III — Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Cont. No. IV — Lack of unity of invention
- ☒ Cont. No. V — Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Cont. No. VI — Certain documents cited
- ☐ Cont. No. VII — Certain defects in the international application
- ☐ Cont. No. VIII — Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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Continuation No. I

Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed.

Continuation No. III:

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of the said claims Nos. 3-9 because said claims Nos. 3-9 relate to the following subject matter which does not require an international preliminary examination (specify):

Although claims 3-9 concern the treatment of the human or animal body by therapy (see PCT Rule 39.1(iv)) the written opinion was carried out and based on the alleged effect.

Continuation No. V

Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims **1-9**	**YES**
	Claims **----**	**NO**
Inventive step (IS)	Claims **1-9**	**YES**
	Claims **----**	**NO**
Industrial applicability (IA)	Claims **1,2**	**YES**
	Claims **3-9**	**NO**

2. Citations and explanations:

The following documents are cited:

D1: The Journal of biological chemistry, 2002, Vol. 277, No. 15, pages 13129-13137

D2: EP 758021 A2
D3: US 6339160 B1

D1 reveals the sequence and the structure of the DM43 glycoprotein. Also the mechanism of the inhibition of the metalloproteinase is disclosed. However, this document does not provide any data which demonstrate that DM43 is a therapeutically active substance which influences apoptosis, cell death or the cell cycle. Thus D1 does not interfere with novelty and inventive step.
D2 is directed to the determining of the therapeutic activity of a peptido-mimetic compound in order to recognise and produce active drugs for treatment of humans and animals. This document concerns pharmaceutical compositions comprising an inhibitor of metalloproteinase as well, but it does not disclose compounds which are comparable with the 43 kD glycoprotein of the present application. Consequently D2 cannot reveal the biological properties of DM43.
Also D3 deals with peptido-mimetic inhibitors of metalloproteinases. However this document concerns organic compounds, that means the production of small chemical compounds which are not DM43.
Although the cited documents teach that inhibitors of metalloproteinases may be useful in medicine (eg. D1 suggests to use DM43 for the treatment of snake envenomation) none of the documents show data which underline that DM43 is really a therapeutically active substance.
Novelty and inventive step are recognized for the subject-matters of all claims.
Industrial applicability is given for the subject-matters of claims 1 and 2. Claims 3-9 concern the treatment of the human or animal body by therapy (see PCT Rule 39.1(iv)). The subject-matters of these claims are not industrially applicable.